Complete Summary

GUIDELINE TITLE

Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update.

BIBLIOGRAPHIC SOURCE(S)

Hollenberg SM, Ahrens TS, Annane D, Astiz ME, Chalfin DB, Dasta JF, Heard SO, Martin C, Napolitano LM, Susla GM, Totaro R, Vincent JL, Zanotti-Cavazzoni S. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med 2004 Sep;32(9):1928-48. [230 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Sepsis
- Septic shock

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Infectious Diseases
Internal Medicine

INTENDED USERS

Health Care Providers
Physicians

GUIDELINE OBJECTIVE(S)

- To provide guidelines for hemodynamic support in sepsis to maintain adequate organ system and cellular perfusion
- To review the state of knowledge concerning hemodynamic therapy of sepsis and to supplement specific therapeutic recommendations with guidelines about how to optimize therapy and how to evaluate the results of therapeutic interventions

Note: Consideration of activated protein C and other therapies not directed at hemodynamic stabilization is outside the scope of these practice parameters.

TARGET POPULATION

Adult patients with sepsis and septic shock

INTERVENTIONS AND PRACTICES CONSIDERED

Monitoring

1. Continuous electrocardiography (ECG)
2. Monitoring of:
    - Heart rate
    - Stroke volume
    - Cardiac output
    - Systemic vascular resistance
    - Indexes of regional or global perfusion
    - Urinary output
3. Pulse oximetry
4. Laboratory measurements
    - Arterial blood gas
    - Serum electrolytes
    - Complete blood count
    - Coagulation variables
    - Lactate concentrations
    - Creatinine clearance
    - Hemoglobin
    - Hematocrit
5. Blood pressure (via arterial cannula)
    - Systolic blood pressure (SBP)
    - Mean arterial pressure (MAP)
6. Hemodynamic assessment (via right heart catheterization)

    - Central venous pressure
    - Central venous oxygen saturation
    - Mixed venous oxyhemoglobin saturation (SVO_2)
7. Glomerular filtration rate
8. Splanchnic blood flow

Hemodynamic Therapy

1. Fluid resuscitation therapy
    - Crystalloids
        - 0.9% sodium chloride (normal saline)
        - Lactated Ringer's solution
        - Hypertonic saline solutions
    - Colloids
        - Plasma protein fraction
        - Albumin
        - Gelatins
        - Dextrans
        - Hydroxyethyl starch
2. Transfusion therapy
3. Vasopressor therapy
    - Dopamine
    - Norepinephrine
    - Phenylephrine
    - Epinephrine
    - Vasopressin
        - Arginine-vasopressin
        - Lysine-vasopressin (terlipressin)
    - Corticosteroids
        - Hydrocortisone
        - Fludrocortisone
        - Methylprednisolone
4. Inotropic therapy
    - Isoproterenol
    - Dopamine
    - Dobutamine
    - Norepinephrine
    - Epinephrine
    - Phosphodiesterase inhibitors (e.g., milrinone)

MAJOR OUTCOMES CONSIDERED

- Mortality
- In-hospital mortality
- Organ dysfunction
- Predictive value of diagnostic tests
- Survival rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The information and recommendations are predicated upon an expert-based review of the available scientific data, clinical investigations, and outcomes research. Where such data are unavailable or limited in scope, consensus was attained by considering published expert opinion and discussion among a wide range of experts.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level I: Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error

Level II: Small, randomized trials with uncertain results; moderate to high risk of false-positive (alpha) error and/or false-negative (beta) error

Level III: Nonrandomized, contemporaneous controls

Level IV: Nonrandomized, historical controls and expert opinion

Level V: Case series, uncontrolled studies, and expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The experts reviewed the literature and classified the strength of evidence of human studies according to study design and scientific value.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations were drafted and graded levels based on an evidence-based rating system (See "Rating Scheme for the Strength of the Recommendations"). The recommendations were debated, and the task force chairman modified the document until <10% of the experts disagreed with the recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendations

J. Supported by at least two level I investigations
K. Supported by only one level I investigation
L. Supported by level II investigations only
M. Supported by at least one level III investigation
N. Supported by level IV or level V investigations only

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The classes of recommendations (A-E) and levels of evidence (I-V) are defined at the end of the "Major Recommendations" field.

Recommendations for Hemodynamic Support of Septic Patients

Basic Principles

1. Resuscitation of patients with sepsis should be initiated expeditiously and pursued vigorously. Measures to improve tissue and organ perfusion are most effective when applied early.
2. Patients with septic shock should be treated in an intensive care unit, with continuous electrocardiographic monitoring and monitoring of arterial oxygenation.

3. Arterial cannulation should be performed in patients with shock to provide a more accurate measurement of intra-arterial pressure and to allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information.
4. Resuscitation should be titrated to clinical end points of arterial pressure, heart rate, urine output, skin perfusion, and mental status, and indexes of tissue perfusion such as blood lactate concentrations and mixed venous oxygen saturation.
5. Assessment of cardiac filling pressures may require central venous or pulmonary artery catheterization. Pulmonary artery catheterization also allows for assessment of pulmonary artery pressures, cardiac output measurement, and measurement of mixed venous oxygen saturation. Echocardiography may also be useful to assess ventricular volumes and cardiac performance.

Fluid Resuscitation

Recommendation 1 - Level B. Fluid infusion should be the initial step in hemodynamic support of patients with septic shock. Initial fluid resuscitation should be titrated to clinical end points.

Recommendation 2 - Level B. Isotonic crystalloids or iso-oncotic colloids are equally effective when titrated to the same hemodynamic end points.

Recommendation 3 - Level D. Invasive hemodynamic monitoring should be considered in those patients not responding promptly to initial resuscitative efforts. Pulmonary edema may occur as a complication of fluid resuscitation and necessitates monitoring of arterial oxygenation. Fluid infusion should be titrated to a level of filling pressure associated with the greatest increase in cardiac output and stroke volume. For most patients, this will be a pulmonary artery occlusion pressure in the range of 12 to 15 mm Hg. An increase in the variation of arterial pressure with respiration may also be used to identify patients likely to respond to additional fluid administration.

Recommendation 4 - Level C. Hemoglobin concentrations should be maintained between 8 and 10 gm/dL. In patients with low cardiac output, mixed venous oxygen desaturation, lactic acidosis, widened gastric-arterial PCO_2 gradients, or significant cardiac or pulmonary disease, transfusion to a higher concentration of hemoglobin may be desirable.

Vasopressor Therapy

Recommendation 1 - Level C. Dopamine and norepinephrine are both effective for increasing arterial blood pressure. It is imperative to ensure that patients are adequately fluid resuscitated. Dopamine raises cardiac output more than norepinephrine, but its use may be limited by tachycardia. Norepinephrine may be a more effective vasopressor in some patients.

Recommendation 2 - Level D. Phenylephrine is an alternative to increase blood pressure, especially in the setting of tachyarrhythmias. Epinephrine can be considered for refractory hypotension, although adverse effects are common, and epinephrine may potentially decrease mesenteric perfusion.

Recommendation 3 - Level B. Administration of low doses of dopamine to maintain renal function is not recommended.

Recommendation 4 - Level C. Patients with hypotension refractory to catecholamine vasopressors may benefit from addition of replacement dose steroids.

Recommendation 5 - Level D. Low doses of vasopressin given after 24 hours as hormone replacement may be effective in raising blood pressure in patients refractory to other vasopressors, although no conclusive data are yet available regarding outcome.

Inotropic Therapy

Recommendation 1 - Level C. Dobutamine is the first choice for patients with low cardiac index and/or low mixed venous oxygen saturation and an adequate mean arterial pressure following fluid resuscitation. Dobutamine may cause hypotension and/or tachycardia in some patients, especially those with decreased filling pressures.

Recommendation 2 - Level B. In patients with evidence of tissue hypoperfusion, addition of dobutamine may be helpful to increase cardiac output and improve organ perfusion. A strategy of routinely increasing cardiac index to predefined "supranormal" levels ($>4.5\ L \cdot min^{-1} \cdot m^{-2}$) has not been shown to improve outcome.

Recommendation 3 - Level C. A vasopressor such as norepinephrine and an inotrope such as dobutamine can be titrated separately to maintain both mean arterial pressure and cardiac output.

Definitions

Level I: Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error

Level II: Small, randomized trials with uncertain results; moderate to high risk of false-positive (alpha) error and/or false-negative (beta) error

Level III: Nonrandomized, contemporaneous controls

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Level V: Case series, uncontrolled studies, and expert opinion

Strength of Recommendations

F. Supported by at least two level I investigations
G. Supported by only one level I investigation
H. Supported by level II investigations only
I. Supported by at least one level III investigation
J. Supported by level IV or level V investigations only

CLINICAL ALGORITHM(S)

A clinical algorithm is provided in the original guideline document for hemodynamic support of adult patients with severe sepsis and septic shock.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for some of the recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

An organized approach to the hemodynamic support of sepsis including use of fluid resuscitation, vasopressor therapy and inotropic therapy

POTENTIAL HARMS

- The primary risk when using hypertonic saline solution is iatrogenically induced hypertonic states due to sodium load.
- There have been reports suggesting that hydroxyethyl starch molecules may adversely affect renal function by causing tubular injury.
- Hydroxyethyl starch can cause dose-dependent decreases in factor VIII activity and prolongation of partial thromboplastin time.
- The major undesirable effects of dopamine are tachycardia and arrhythmogenesis, both of which are more prominent than with other vasopressor agents. Other side effects include increased pulmonary artery occlusion pressure, increased pulmonary shunt, and the potential for decreased prolactin release and consequent immunosuppression.

Complications of Fluid Resuscitation Therapies

- The major complications of fluid resuscitation are pulmonary and systemic edema. These complications are related to three principal factors: a) increases in hydrostatic pressures; b) decreases in colloid osmotic pressure; and c) increases in microvascular permeability associated with septic shock. The controversy concerning crystalloid and colloid resuscitation revolves around the importance of maintaining plasma colloid osmotic pressure. Large volume crystalloid resuscitation results in significant decreases in plasma colloid osmotic pressure, whereas plasma colloid osmotic pressure is maintained with colloid infusion. In experimental studies, decreases in plasma colloid osmotic pressure increase extravascular fluid flux in the lungs and lower the level of hydrostatic pressure associated with lung water

accumulation. Some, but not all, clinical reports have observed a correlation between decreases in the colloid osmotic pressure-pulmonary artery occlusion pressure gradient and the presence of pulmonary edema. Several clinical studies have randomized subjects to crystalloid or colloid infusion and examined the development of pulmonary edema with mixed results, demonstrating either no differences between solutions or an increased incidence of pulmonary edema with crystalloids. Experimental reports in septic models demonstrate no increase in extravascular lung water when hydrostatic pressures are maintained at low levels, indicating that in sepsis the primary determinant of extravascular fluid flux appears to be microvascular pressure rather than colloid osmotic pressure. Together, these data suggest that when lower filling pressures are maintained there is no significant difference in the development of pulmonary edema with crystalloids or colloids. However, if higher filling pressures are required to optimize cardiac performance in patients with ventricular dysfunction, colloids may mitigate against extravascular fluid flux.

- The acute respiratory distress syndrome occurs in 30-60% of patients with septic shock. Of concern has been the possibility that in the setting of increased microvascular permeability, colloid particles could migrate into the interstitium where they would favor fluid retention in the lung and worsen pulmonary edema. A number of studies, including a variety of models of increased microvascular permeability, as well as clinical studies in patients with septic shock and the acute respiratory distress syndrome, have not found evidence of increased lung water or compromised lung function with colloids.
- Systemic edema is a frequent complication of fluid resuscitation. The relative roles of increased microvascular permeability, increases in hydrostatic pressure, and decreases in plasma colloid osmotic pressure in the development of this complication during sepsis are unclear. Tissue edema may reduce tissue oxygen tensions by increasing the distance for diffusion of oxygen into cells. During experimental peritonitis, crystalloid therapy was associated with increased endothelial cell swelling and decreased systemic capillary cross-sectional area when compared with colloid infusion. In contrast, other studies comparing the impact of large volume crystalloid infusion on skeletal muscle and intestinal oxygen metabolism have observed no impairment of oxidative metabolism despite significant edema formation. The integrity of the gastrointestinal mucosa as a barrier to bacterial translocation also does not appear to be affected by decreases in colloid osmotic pressure and the development of tissue edema following crystalloid resuscitation. A comparison of crystalloid and colloid resuscitation in thermal injury found that the extent of resuscitation and not the choice of fluids was the major determinant of bacterial translocation.
- Finally, there have been multiple meta-analyses of the clinical studies comparing crystalloids with colloids, which have examined the effect of resuscitation with these solutions on mortality rate. The results have been conflicting, with some of the reports suggesting differences in mortality rate favoring crystalloids, whereas others have shown no differences. These differences reflect the poor quality of many of the underlying studies, the heterogeneity in patient populations, and the

fact that none of the clinical studies was ever designed with mortality as an end point.

Complications of Vasopressor Therapy

- All of the catecholamine vasopressor agents can cause significant tachycardia, especially in patients who are inadequately volume resuscitated. Tachyarrhythmias can occur as well. In patients with significant coronary atherosclerosis, vasopressor-induced coronary artery constriction may precipitate myocardial ischemia and infarction; this is of particular concern in patients treated with vasopressin. In the presence of myocardial dysfunction, excessive vasoconstriction can decrease stroke volume, cardiac output, and oxygen delivery. Should this occur, the dose of vasopressor should be lowered, or the addition of an inotropic agent such as dobutamine should be considered. Vasopressors can also cause limb ischemia and necrosis.
- Administration of vasopressors may impair blood flow to the splanchnic system, and this can be manifested by stress ulceration, ileus, malabsorption, and even bowel infarction. Gut mucosal integrity occupies a key position in the pathogenesis of multiple organ failure, and countercurrent flow in splanchnic microcirculation gives the gut a higher critical threshold for oxygen delivery than other organs. If possible, episodes of intramucosal acidosis, which might be detected either by a decrease in gastric mucosal pHi or an increase in gastric mucosal PCO_2, should be avoided, although no prospective randomized controlled trial has demonstrated a decrease in mortality rate with pHi or gastric PCO_2-directed care in the management of patients with septic shock.

Complications of Inotropic Therapy

- In the septic patient who has been inadequately volume resuscitated, all of the inotropic agents can cause significant tachycardia and other cardiac arrhythmias. In patients with coexisting coronary disease, the change in myocardial oxygen consumption may precipitate myocardial ischemia and infarction. Excessive doses of catecholamines can also result in myocardial band necrosis independent of the presence of coronary disease.
- Sole use of inotropic agents that also have vasodilatory activity (e.g., isoproterenol, milrinone) is likely to reduce blood pressure. These reductions can be long-lasting with agents that have long half-lives.
- Administration of inotropic agents that have pressor activity may impair blood flow to other organ beds, such as the splanchnic circulation. Efforts to ensure adequate volume resuscitation and to assess end-organ function must be made.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These guidelines are for adult patients and do not cover all conceivable clinical scenarios.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hollenberg SM, Ahrens TS, Annane D, Astiz ME, Chalfin DB, Dasta JF, Heard SO, Martin C, Napolitano LM, Susla GM, Totaro R, Vincent JL, Zanotti-Cavazzoni S. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med 2004 Sep;32(9):1928-48. [230 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Sep

GUIDELINE DEVELOPER(S)

Society of Critical Care Medicine - Professional Association

SOURCE(S) OF FUNDING

Society of Critical Care Medicine (SCCM)

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Society of Critical Care Medicine (SCCM) Web site.

Print copies: Available from the Society of Critical Care Medicine, 701 Lee Street, Suite 200, Des Plaines, IL 60016; Phone: (847) 827-6869; Fax: (847) 827-6886; on-line through the SCCM Bookstore.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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